

**THE NEURAL CORRELATES OF EMOTIONAL NUMBING AND NICOTINE USE IN
VETERANS DURING WAKE AND REM: AN [¹⁸F]-FDG PET IMAGING STUDY**

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Confirmatory factor analyses and theories of posttraumatic stress disorder (PTSD) support the clinical and scientific relevance of a distinct emotional numbing construct in PTSD. Increased emotional numbing has been linked with increased nicotine use. Deficits in reward system functioning may be related to symptoms of emotional numbing and nicotine use. Previous research has found altered neurotransmitter function and brain activation in response to reward in reward system brain structures in PTSD. In normal REM sleep, these brain structures have increased activity and are related to sleep-wake mechanisms, which may be dysregulated in PTSD. This study used polysomnography (PSG) and [¹⁸F]-FDG PET imaging to conduct region of interest analyses (ROIs) examining possible resting state brain activity deficits in Operation Enduring Freedom and Operation Iraqi Freedom veterans in the striatum and amygdala. It was hypothesized that 1) increased emotional numbing would be associated with decreased activity during wakefulness and REM; 2) increased emotional numbing would be associated with increased nicotine use; and 3) increased nicotine use would be associated with decreased activity during wakefulness and REM. Results indicate that increased emotional numbing corresponds with decreased activity during wakefulness in the striatum and amygdala, but not after adjusting for all non-emotional numbing symptoms of PTSD. This pattern was reversed during REM, with increased emotional numbing corresponding with increased activity in the striatum, which survived adjusting for non-emotional numbing symptoms of PTSD. Emotional numbing was not

correlated with nicotine use, possibly because heavy smokers were underrepresented in the sample. Increased nicotine use was associated with decreased activity during wakefulness in the striatum, but was not related to activity during REM. Results support the involvement of reward structures in nicotine use, emotional numbing, and other symptoms of PTSD. Dysregulation in the reward system may exaggerate patterns of activity seen in healthy adults, with less activity in reward structures during quiet wakefulness and increased activity during REM sleep.

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1.0 INTRODUCTION

Posttraumatic Stress Disorder (PTSD) is a serious psychological disorder currently defined by the persistence of three clusters of seventeen total symptoms for at least one month following a traumatic experience, which causes significant distress or impairment in functioning. The re-experiencing cluster (criteria B1-B5) contains symptoms such as intrusive recollections of the traumatic event, reactivity to trauma-related cues, and nightmares of the traumatic event. The avoidance and numbing cluster (criteria C1-C7) includes items such as avoidance of trauma-related cues, restricted affect, and diminished interest in activities. Finally, the hyperarousal cluster (criteria D1-D5) contains such symptoms as insomnia, hypervigilance, and exaggerated startle response (American Psychiatric Association, 2000). (See Table 1 for a complete listing of all seventeen symptoms). Trauma associated with combat exposure and service in the military is a significant risk factor for PTSD. More than 1.7 million men and women have served in the United States military in support of Operation Enduring Freedom in Afghanistan (OEF) and Operation Iraqi Freedom (OIF) since 2001 (Sollinger, Fisher & Metscher, 2008), and estimates of overall PTSD prevalence among OEF/OIF veterans range from 10 to 15 percent (Ramchand et al., 2011). There is thus a particular impetus to understand the psychological factors and biological mechanisms which contribute to PTSD in OEF/OIF veterans.

Although the current diagnostic criteria for PTSD presents a three factor model of PTSD symptoms, previous research on the factor structure of PTSD has supported a four factor model that divides the symptoms of PTSD into re-experiencing, avoidance, hyperarousal and emotional numbing (King et al., 1998; Asmundson, Stapleton, & Taylor, 2004). This model separates the

single DSM-IV-TR avoidance and numbing symptom cluster into separate avoidance and emotional numbing clusters, with the empirically-based emotional numbing construct consisting of amnesia for the traumatic event, diminished interest in activities, detachment from others, restricted affect, and a sense of foreshortened future. The DSM-IV-TR offers a narrower theoretical definition of emotional numbing which includes only diminished interest, detachment, and restricted affect (American Psychiatric Association, 2000).

According to Litz and Gray's (2002) theory of emotional numbing, the symptoms of emotional numbing do not reflect a complete inability of PTSD patients to experience positive emotions. Rather, PTSD patients retain their complete pre-traumatic emotional capacity, but positive emotional responses become harder to access due to the salience of post-traumatic negative emotional responses, particularly in the presence of trauma-related cues and re-experiencing symptoms. This suggests that symptoms of PTSD may be phasic, with re-experiencing symptoms triggering periods of heightened emotional numbing, while hyperarousal symptoms further deplete emotional and cognitive resources necessary for positive emotions by redirecting attention to threat and anxiety cues. Stein and Paulus (2009) characterized the distinction between emotional numbing and the other three clusters of re-experiencing, avoidance and hyperarousal as a dysregulation in the homeostatic balance between the approach and avoidance systems. Emotional numbing is conceptualized as the result of dysfunction in reward processes leading to a downregulation of approach, while the remaining symptom clusters are conceptualized as the products of dysfunction in fear-related processes leading to an upregulation of avoidance. Together, these theories provide a context for the importance of emotional numbing in PTSD and its relation to the other symptom clusters.

Emotional numbing is thus an important construct in PTSD symptomology, and is also present in other disorders, such as depersonalization disorder (Sierra et al, 2005). Emotional numbing is a predictor of chronic PTSD (Feeny et al., 2000) and is positively correlated with higher levels of alcohol misuse (Jakupcak et al., 2012), nicotine use (Kirby et al., 2008; Cook et al., 2009; Greenberg et al., 2012), sexual dysfunction (Nunnink et al., 2010), non-adherence to psychotherapy (Angeli, 2009), violent behaviors (Maguen et al., 2009), and poorer interpersonal relationships (Beck et al., 2009). Empirical evidence also supports the existence of an emotional numbing construct in PTSD separate from depression (Feeny et al., 2000). Furthermore, emotional numbing has been identified as a significant factor of PTSD in western and non-western cultures and in civilian and military samples, indicating a broad significance and applicability beyond American military service members (Costa et al., 2011).

Despite the clinical relevance of emotional numbing, there is limited data on its neurobiological underpinnings. Previous research on the neural correlates of PTSD suggests that underactivation in the medial prefrontal cortex (mPFC) may lead to overactivation in the amygdala due to less inhibition via downward projections from the mPFC to the amygdala (Koenigs & Grafman, 2009). The amygdala is a critical structure in regulating fear responses, and dysregulation of the amygdala may explain chronic fear-related symptoms in PTSD. However, this model may not fully account for symptoms of emotional numbing, particularly anhedonia (Garfinkel & Liberzon, 2009). Recent research has examined the role of the reward system in PTSD, since dysregulation in this system may explain symptoms of emotional numbing. Two previous fMRI studies have found lower levels of activation in response to reward in the reward system of PTSD patients relative to controls. Sailer et al. (2008) found less activation in the nucleus accumbens, thalamus, and mesial PFC of 13 women with PTSD due to

various traumas, as compared to healthy controls. Elman et al. (2009) found less activation in the striatum, defined as the nucleus accumbens, caudate nucleus, and putamen, in 20 civilian men and women with PTSD due to various traumas, as compared to healthy controls. Elman et al. (2009) additionally found that less activation in the striatum in response to reward was correlated with increases in two symptoms of emotional numbing, namely diminished interest and detachment. However, striatal activation was not correlated with restricted affect or sense of foreshortened future. PTSD patients also demonstrated a non-significant trend towards less striatal deactivation in response to monetary loss, as compared to controls.

Further support for the potential importance of the reward system in PTSD comes from Liberzon et al. (2007), who examined μ -opioid receptor binding potential (BP2) in healthy controls, combat-exposed controls, and combat-exposed PTSD patients using positron emission tomography (PET) and the radioactive opioid [^{11}C] carfentanil tracer. They found that both combat-exposed groups had lower BP2 than healthy controls in the nucleus accumbens and extended amygdala, as well as the dorsal frontal and insular cortex. Reduced BP2 was found in the anterior cingulate cortex of PTSD patients relative to both non-PTSD groups, and in the amygdala of combat-exposed controls relative to PTSD patients and healthy controls. PTSD patients had a higher BP2 in the orbitofrontal cortex than healthy controls. Combat-exposed controls had a higher BP2 in the orbitofrontal cortex and lower BP2 in the amygdala than both PTSD patients and healthy controls. These regions are involved in reward and emotional processes, and abnormal opioid receptor functioning in these areas may contribute to emotional numbing and anhedonia.

Consistent with the finding of altered opioid receptor functioning in PTSD, animal research has shown that inescapable stress produces increased opioid release in the presence of

trauma-related cues causing conditioned analgesia (Hyson et al., 1982). Foa, Zinbarg, and Rothbaum (1992) argued that this phenomenon approximates emotional numbing in humans with PTSD, and that analgesia in PTSD patients may be one manifestation of emotional numbing. Evidence of conditioned analgesia in PTSD patients supports this hypothesis (Pitman et al, 1990; Diener et al., 2012).

Complementary to the finding of opioid-mediated analgesia in PTSD, it has also been hypothesized that a depletion of catecholamines, particularly norepinephrine and dopamine, may account for emotional numbing (van der Kolk et al., 1985). Dopamine within the reward system is associated with positive emotions and feelings of pleasure, and opioid release triggers catecholamine release, causing an initial increase in dopamine followed by a period of depletion.

These theories postulate that there may be alternating periods of increased and subsequently decreased opioid and catecholamine activity which relate to symptoms of emotional numbing. The mixed evidence from preliminary evaluations of opiate antagonists and dopamine agonists provides some highly circumstantial evidence that either may potentially alleviate some symptoms of PTSD under the correct conditions. A preliminary study of the opiate antagonist nalmefene found a decrease in PTSD symptoms, including emotional numbing, in a small, uncontrolled sample of veterans (Glover, 1993). The opiate antagonist naltrexone was found effective in reducing flashbacks in two case studies of an adult male and female (Bills & Kreisler, 1993). However, there is no convincing support for the effects of nalmefene, and a preliminary study of naltrexone did not find clinically significant decreases in any PTSD symptoms (Lubin et al. 2002). Furthermore, opiate antagonists may actually increase symptoms of PTSD after initial administration (Glover, 1995). These mixed findings may indicate fluctuating levels of natural opioid release in the reward system, so that opioid antagonists

reduce symptoms during periods of increased opioid release (such as in the presence of a trauma-related cue), but not otherwise. There is also preliminary support for the hypothesis that PTSD may include at least periodic catecholamine depletion. In three case studies of PTSD treatment with psychostimulants, Houlihan (2011) saw improvement in overall functioning and PTSD symptoms in three military veterans. One veteran specifically reported improvements in symptoms of emotional numbing, consistent with the hypothesis that emotional numbing may be caused by catecholamine depletion. However, these results have yet to be replicated and subjected to vigorous, controlled evaluation.

In addition to psychostimulants, substances of abuse are also known to alter functioning in the reward system by triggering the release of mesolimbic dopamine (Blum et al., 2000), and 21.7% of military veterans with PTSD have been found to have a comorbid substance abuse disorder (Petrakis, Rosenheck, & Desai, 2011). Likewise, alcohol and nicotine use affect mesolimbic dopamine reward system function and are prevalent in civilians and military personnel with PTSD (Blum et al., 2000). Furthermore, Jakupcak et al. (2010) found that emotional numbing symptoms were more strongly associated with alcohol misuse than other symptom clusters in OEF/OIF veterans, and that this relationship persisted after controlling for depression. However, Maguen et al. (2009) found that only re-experiencing symptoms of PTSD predicted post-deployment problem drinking in veterans of the peacekeeping assignment in Kosovo.

Three studies have linked nicotine use and symptoms of emotional numbing. Kirby et al. (2008) found that among male OEF/OIF veterans with PTSD, current smokers had significantly higher symptoms of emotional numbing, but were statistically equal with non-smokers in all other symptom clusters. Cook et al. (2009) found that veterans (with and without a diagnosis of

PTSD) with higher levels of overall PTSD severity were more likely to report heavy smoking (greater than or equal to 20 cigarettes per day), as were veterans with higher levels of emotional numbing. None of the other symptom clusters of PTSD predicted smoking. Greenberg et al. (2012) found that emotional numbing was the only symptom cluster to significantly predict lifetime smoking in U.S. adults with a trauma history after controlling for all other symptom clusters and demographic variables. However, no clusters were uniquely associated with lifetime cigarettes per day, defined as the highest number of cigarettes smoked on a “usual” day. The use of substances of abuse, alcohol and nicotine in veterans with PTSD may reflect an attempt to stimulate an underactive reward system (Blum et al., 2000), and the same underactivity may also contribute to emotional numbing.

The preceding evidence suggests that there may be associations between emotional numbing, nicotine use, and reward system activity during wakefulness in PTSD. In addition, there is also reason to suspect that neurobiological functioning in sleep influences symptoms of PTSD, including emotional numbing. Sleep disturbances, i.e. insomnia and nightmares, are among the most commonly reported symptoms of PTSD (Green, 2003), indicating that the neurobiological mechanisms responsible for PTSD can also alter sleep-wake brain mechanisms. Sleep deprivation has been shown to increase reactivity to both positive and negative stimuli in healthy adults, and can increase feelings of anxiety and negatively affect mood (Talbot et al., 2010). Using fMRI techniques, Gujar et al. (2011) observed increased activation in response to reward following sleep deprivation in the ventral tegmental area, left putamen, amygdala, and left insular cortex, while Venkatraman et al. (2007; 2011) observed increased activation in the right nucleus accumbens and ventral striatum, and decreased activation in the insular and orbitofrontal cortices, indicating a greater response to reward and a lesser response to loss. Sleep

regulation and reward processing in the mesolimbic pathway are jointly influenced by orexin projections from the lateral hypothalamus, which may mediate the relationship between sleep and reward (Harris, Wimmer, and Aston-Jones, 2005; Sakurai, 2007). This indicates that mesolimbic activity during sleep may be of relevance to the neurobiological model of PTSD, particularly during rapid eye movement sleep (REM).

In healthy REM sleep, there is a relative increase in glucose metabolism compared to quiet wakefulness in brain structures relevant to reward processing and PTSD, including the amygdala, ventral striatum, and orbitofrontal and cingulate cortices (Nofzinger et al., 1998). Dysregulation in REM sleep thus has the potential to affect reward processing and symptoms of PTSD, including emotional numbing, and may contribute to nicotine use.

This study used [^{18}F]-fluorodeoxyglucose (FDG) PET in conjunction with polysomnography (PSG) in order to investigate the neural correlates of emotional numbing, nicotine use, and relative regional cerebral metabolic rate of glucose (rCMRglc) in both quiet wakefulness and REM among OEF/OIF veterans, with a primary focus on brain regions of the reward system. Due to previous findings of less activation in the reward system in response to reward in adult PTSD patients (Sailer et al., 2008; Elman et al., 2009), in addition to the dysregulation of neurotransmitters implicated in reward and emotional processing, it was firstly hypothesized that there would be a negative correlation between emotional numbing and relative rCMRglc in wakefulness and REM in reward structures. Based on the previous findings of increased nicotine use with increased emotional numbing (Kirby et al., 2008; Cook et al. 2009; Greenberg et al., 2012), it was secondly hypothesized that nicotine use and severity of emotional numbing symptoms would be positively correlated. It was thirdly hypothesized that there would be a negative correlation between nicotine use and relative rCMRglc in wakefulness and REM in

rewards structures, as nicotine use may represent an attempt to stimulate a dysregulated reward system.

2.0 METHODS

2.1 PARTICIPANTS

Data were collected from participants enrolled in one of two study protocols (Grant PT073961-W81XWH-07-PTSD-IIRA and Grant MH083035) conducted by the Veterans Sleep Studies in the Department of Psychiatry at the University of Pittsburgh between June 2008 and October 2011. Procedures for both protocols were approved by the University of Pittsburgh, Institutional Review Board and the Human Use Subcommittee of the Radioactive Drug Safety Committee. Written informed consent was obtained from participants before being enrolled in the study and compensation was provided. Eligible participants were 18-50 year old male and female OEF/OIF veterans recruited through local media advertising and military-focused health fairs. Participants were excluded for a diagnosis of current, untreated severe depression, history of substance or alcohol abuse or dependence within three months prior to study enrollment, significant or unstable acute or chronic medical conditions, history of traumatic brain injury or current concussive symptoms, current sleep disorders other than insomnia or nightmares, a traumatic experience within three months prior to study enrollment, presence of implanted devices or metal in the body, fear of enclosed spaces, previous radiation exposure within the past year exceeding recommended safety limits, pregnancy or breastfeeding, and unexpected, untreated, or serious EKG findings. In addition, participants had not taken medications known to

affect sleep or wake function within a minimum of two weeks prior to beginning study procedures. Sobriety was required during all study procedures. Participants were requested not to consume more than four cups of coffee or the caffeine-equivalent per 24 hour period, and no more than two alcoholic drinks per day, or more than 14 drinks per week on average. Participants were permitted to remain in ongoing counseling services they may have been receiving prior to study enrollment, but were excluded if they were receiving cognitive behavioral therapy for PTSD.

2.2 ASSESSMENTS

Psychiatric symptoms were assessed by a research clinician during a diagnostic interview using the following standardized assessments:

Structured Clinical Interview for DSM-IV (SCID) – The SCID assesses current and past symptoms of DSM-IV disorders, including mood, anxiety, psychotic, alcohol, substance, somatic, and eating disorders (First et al., 1996).

Structured Interview for DSM-IV Sleep Disorders (SID-SD) – The SID-SD assesses the presence, frequency, and severity of current and past symptoms of DSM-IV sleep disorders, as well as other common sleep disorders including obstructive sleep apnea and restless leg syndrome.

Clinician Administered PTSD Scale-Part 1 (CAPS) – The CAPS assess the frequency and intensity of the 17 DSM-IV diagnostic criteria for PTSD (Weathers, Keane, & Davidson, 2001). This study utilized the CAPS to assess past month and lifetime PTSD symptoms. A minimum score of one for frequency and two for intensity was required of an item to contribute to a diagnosis of PTSD. Per the emotional numbing factor of King et al. (1998), an emotional

numbing scale was created by summing the frequency and intensity scores of items 8-12 (C3-C7), yielding a possible emotional numbing score 0-40 with higher scores indicating greater endorsement of emotional numbing symptoms. A non-emotional numbing scale was created by summing the frequency and intensity scores of the remaining items (1-7, 13-17), yielding a possible non-emotional numbing score 0-96, which was used as a covariate to control for PTSD severity among all symptoms other than emotional numbing. The emotional numbing and non-emotional numbing scales are summarized in Table 1.

Pittsburgh Sleep Quality Index (PSQI) – The PSQI is a self-report measure of past month subjective sleep quality with higher scores indicating lower quality sleep. Scores less than 5 indicate good quality sleep (Buysse et al., 1989).

Beck Depression Inventory (BDI) – The BDI is a self-report questionnaire that assesses the severity of depression symptoms, with scores of 13 and below indicating minimal depression (Beck, Steer, & Brown, 1996).

Table 1. PTSD symptoms included on emotional numbing and non-emotional numbing scales

	Emotional Numbing Scale	Non-Emotional Numbing Scale
Range	0-40	0-96
Items	C-3 Inability to recall important aspects of trauma C-4 Diminished Interest C-5 Detachment from others C-6 Restricted Affect C-7 Sense of foreshortened future	B-1 Intrusive recollections of trauma B-2 Nightmares B-3 Flashbacks B-4 Psychological distress to trauma cues B-5 Physiological reactivity to trauma cues C-1 Avoidance of trauma-related thoughts C-2 Avoidance of trauma-related cues D-1 Insomnia D-2 Irritability D-3 Difficulty concentrating D-4 Hypervigilance D-5 Exaggerated startle response

Combat exposure was measured with the Combat Exposure Scale (CES), which is a seven item self-report questionnaire that assesses the frequency of dangerous combat experiences. Scores range from 0-41, with higher scores indicating a higher frequency of dangerous combat experiences (Keane et al., 1989).

Sleep and substance use behaviors were assessed for one to two weeks following the diagnostic interview, using the Pittsburgh Sleep Diary (PghSD) (Monk et al., 1994). Participants recorded their behavior in the PghSD twice per day. In the morning, participants reported on their previous nights' sleep, including sleep quantity and quality measures. Habitual bedtimes and rising times were calculated from this sleep diary data. In the evening, participants reported on their sleep-related activities during the day, including their caffeine intake, nicotine and alcohol use, and other medication use. Average daily use of caffeine, nicotine and alcohol was

computed from PghSD reports. Although participants were supposed to complete the PghSD for 7-14 days, the prospective, self-report nature of the PghSD makes it difficult to ensure that participants complete it fully. In the case that a diary was not fully completed, data was obtained and averaged according to the days that were completed. In total, seven participants provided less than seven days of PghSD data. Three of these participants provided six days of data, two provided five days of data, and two provided four days of data. No participants provided less than four days of PghSD data. Participants additionally completed a urine drug screen and breathalyzer test before completing study procedures to verify sobriety. Smoking was not permitted during imaging procedures or between the participant's habitual bedtime and morning awakening time while completing a sleep study, but was not otherwise restricted.

In addition, a sleep screening study was completed in the University of Pittsburgh Neuroscience and Clinical Translational Research Center (NCTRC) (Grant UL1RR024153) to verify the absence of obstructive sleep apnea or any other exclusionary sleep disorders.

Physical health was assessed by a study physician during a physical evaluation including a medical history questionnaire, a traumatic brain injury screening questionnaire, a blood draw to test blood chemistry, a urine drug screen, and an EKG. Included participants did not endorse any current concussive symptoms or other significant medical conditions.

Additionally, magnetic resonance imaging (MRI) was used to assess any potential brain pathology and served for co-registration with PET images. An MRI scan was completed at the University of Pittsburgh Magnetic Resonance Research Center (MRRC) using a Siemens 3T Trio scanner. An axial series oriented to the anterior-posterior commissure line with a 5mm section thickness/1mm intersection gap was used to detect structural brain anomalies. A volumetric MPRAGE sequence was obtained in the sagittal plane, which was optimized for maximal

contrast between brain matters and used a high resolution slice thickness of 1.5/1.2mm, 0mm interslice. This image served for MR-guided region of interest (ROI) placement and co-registration with PET images via Automated Image Restoration (AIR).

2.3 POLYSOMNOGRAPHY AND PET PROCEDURES

PSG and PET procedures were conducted according to validated methods (Nofzinger et al., 1998). Participants stayed overnight in the NCTRC a minimum of four nights, including the sleep screening study. Figure 1 provides a graphic overview of the experimental protocol. On each experimental night, participants were monitored via PSG, including bilateral central and occipital EEG channels, EOG, and submentalis EMG, and had intravenous tubing placed in each arm to allow for accommodation and administration of the [^{18}F]-FDG and to sample blood radiation levels following injection. Participants were instructed to go to bed each night at their habitual bedtime, as determined by PghSD data. Participants completed two PET scans over the four nights in the lab. The first scan assessed relative rCMRglc in wakefulness, while the second scan assessed relative rCMRglc in REM.

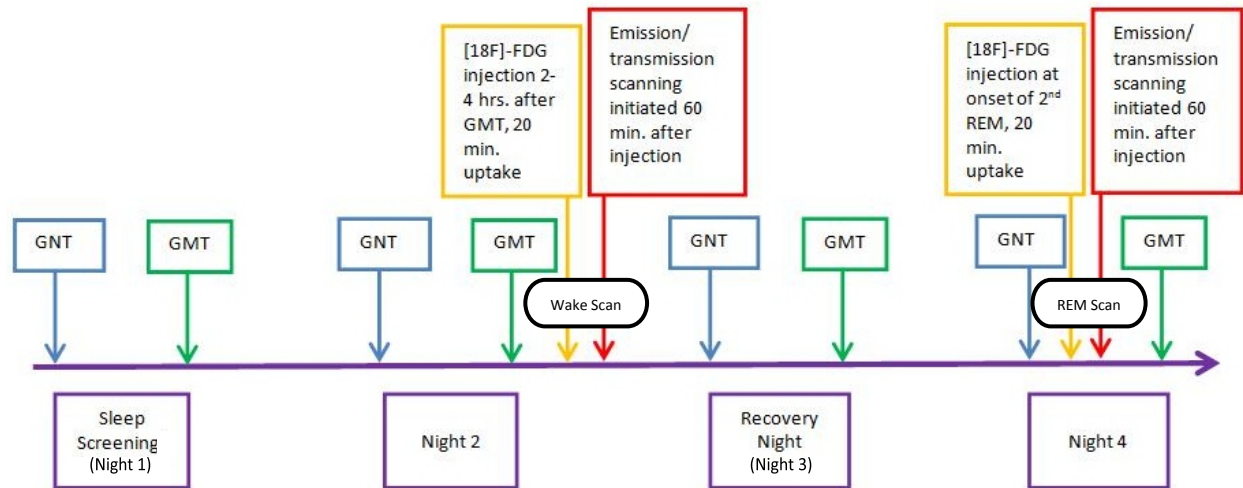


Figure 1. Timeline of PET procedures

GNT = habitual bedtime; GMT = habitual awakening time.

In order to optimize alertness during the wake scan, the first [^{18}F]-FDG injection occurred two to four hours after the habitual wake time following Night 2. Participants were instructed to lie supine with their eyes closed while still being monitored by PSG to ensure wakefulness. After a 15 minute accommodation period, participants were injected with the [^{18}F]-FDG through the intravenous catheter already in place. The uptake of [^{18}F]-FDG is complete at 20 minutes, and is 70-80% maximal in the first 12 minutes (Nofzinger et al., 1998). Participants thus remained in a state of quiet wakefulness for an additional 20 minutes following the injection. After the completion of the uptake period, participants were transported from the NCTRC to the PET center facilities, where scans were completed using a Siemens/CTI ECAT HR+ scanner with a Neuro-insert (CTI PET Systems, Knoxville, TN) in 3D mode. Sixty minutes after injection time, a series of six sequential five minute emission scans was begun, allowing for a composite 30 minute scan which excluded data corrupted by movement. The emission scans were followed by a 15 minute transmission scan to allow for quantitative correction of attenuation.

After completing the wake scan, participants completed a recovery night in the NCRTC without a PET scan. On the fourth night, injection of [^{18}F]-FDG was made at the onset of the second REM period, as indicated by PSG. The participant was awoken 20 minutes after the injection and the same scanning procedures following the injection during wakefulness were repeated. The participant was then allowed to return to the NCRTC and sleep ad lib through the morning.

2.4 IMAGE ANALYSES

PET scans were considered valid if participants remained in the target state for at least 10 minutes after injection and did not move during the scan. One to two non-contiguous epochs of a state which was not the target state were allowed within the first 10 minutes. Although injection times were chosen to optimize state consistency, states can change quickly and sleep in veterans tends to be particularly fragmented. However, uptake of [^{18}F]-FDG is low after the initial 10 minute uptake period, so PET scans still approximate the stage maintained in the first 10 minute period, regardless of state inconsistency in the second 10 minutes of uptake (Nofzinger et al., 1998). Brain/non-brain segmentation was applied to the MR data to create a brain tissue mask for sampling the PET data for the purpose of whole brain normalization of regional metabolic rate of deoxyglucose (MRDglc). Absolute brain glucose metabolism was estimated based on six venous plasma samples collected every 8 minutes starting 45 minutes after [^{18}F]-FDG injection. This was used to correct for between subject variability. The relative regional cerebral metabolic rate of glucose (rCMRglc) value served as the primary measure of neuronal activity level. PET images were reconstructed using standard commercial software as

63 transaxial slices (center to center 2.4 mm) with approximate 6mm full-width, half-maximum resolution. Automatic Image Restoration software was used to co-register PET and MR image sets. MR and PET images were then translated in Montreal Neurological Institute (MNI) space according to standard equations to allow for between subject comparisons.

2.5 STATISTICAL ANALYSES

Demographic and clinical variables were summarized and compared using SPSS 19 software. Independent sample t-tests and chi-square tests were used to compare PTSD with non-PTSD patients, nicotine with non-nicotine users, and males with females within both samples. Correlations among continuous variables were computed using Pearson correlations. Statistical Parametric Mapping version 8 (SPM8) (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) was used to conduct negative and positive correlational analyses between relative rCMRglc and emotional numbing and daily average nicotine use within the wake and REM samples. The emotional numbing correlations were also repeated using non-emotional numbing as a covariate. Region of interest analyses (ROIs) were conducted for the striatum, defined as the bilateral caudate, putamen and nucleus accumbens. ROIs were also conducted for the bilateral amygdala. If a statistically significant cluster of contiguous voxels was found within these structures, ROIs were conducted for the individual structures within the larger ROI structure (e.g. right/left striatum, right/left caudate, right/left putamen, right/left nucleus accumbens, right/left amygdala) in order to further localize the cluster. Given the a priori nature of the hypotheses under scrutiny, statistical significance of clusters within the ROIs was assessed using the uncorrected p value

(p_{uncorr}) of the maximum voxel of significance. A maximum of $p_{\text{uncorr}}=0.01$ was used as a cut off for significance.

Exploratory whole brain correlational analyses were also conducted. The results of these analyses are presented in Appendix A as supplementary material. A maximum cluster-level uncorrected p value of $p_{\text{uncorr}}=0.05$ was permitted in order to include a cluster in the results, but the more stringent cluster-level family-wise corrected p value ($p_{\text{fwe-corr}}$) was also reported. These clusters received alphabetic labels for ease of identification.

3.0 RESULTS

3.1 SAMPLE CHARACTERISTICS

Thirty six participants met inclusion criteria and completed at least one valid [^{18}F]-FDG PET scan. Twenty five participants completed valid wake and REM scans, nine participants only completed a valid wake scan, and two participants only completed a valid REM scan. Participants who completed a valid wake scan comprised the wake sample ($n=34$) and participants who completed a valid REM scan comprised the REM sample ($n=27$).

3.1.1 Demographics

3.1.1.1 Wake Sample

Thirty four participants met inclusion criteria and completed a valid [^{18}F]-FDG PET scan during wakefulness. The demographic and clinical characteristics of this sample are summarized in Table 2. Participants were 22 to 45 years old and Caucasian males comprised the majority of the sample. Combat exposure ranged from light to heavy combat, with an average combat exposure of light-moderate ($Mean=15.47$, $SD=10.60$). Average emotional numbing and non-emotional numbing were moderate for the PTSD sample ($Mean=13.38$, $SD=6.10$; and $Mean=44.69$, $SD=11.03$) and low for the non-PTSD sample ($Mean=2.83$, $SD=3.97$; and $Mean=12.39$, $SD=8.13$). Emotional numbing scores ranged from 0-25 in the PTSD sample and 0-13 in the

non-PTSD sample. The distribution of emotional numbing scores for each sample is displayed in Figure 2. There were non-significant trends for females to have higher emotional numbing and non-emotional numbing scores than males. Within the entire wake sample, average symptoms of depression were mild, with a mean BDI score of 5.32 ($SD= 4.98$) well below the clinical cut off of 13. Sleep difficulties were mild to moderate within the wake sample, with a mean PSQI score of 5.74 ($SD=3.65$) slightly above the clinical threshold score for good sleep. PTSD patients had moderately poor sleep with a mean PSQI score of 8.13 ($SD=3.50$) versus non-PTSD patients who had relatively good sleep with a mean PSQI score of 3.61 ($SD = 2.20$). Average daily nicotine, alcohol and caffeine use were low within the entire wake sample. A verage daily nicotine use for the nicotine user sample was moderate with a mean of 7.75 doses per day ($SD=5.23$). Because there were only five females and five non-Caucasians in the wake sample, gender and race differences could not be explored.

Table 2. Wake sample demographic and clinical characteristics

	Whole Group	PTSD	Non-PTSD	Nicotine Users	Non-Nicotine Users
<i>n</i>	34	16	18	13	21
Age Mean (Range)	29.75 (22-45)	29.52 (22-40)	29.95 (23-45)	30.75 (22-40)	29.13 (22-45)
Percent Females	14.71	25.00	5.56	23.08	9.52
Percent Caucasian	85.29	81.25	88.89	76.92	90.48
Percent PTSD	47.06	100.00	0.00	46.15	47.62
Emotional Numbing Mean (SD)	7.79 (7.32)	13.38 (6.10)*	2.83 (3.97)*	8.08 (6.89)	7.62 (7.74)
Non-Emotional Numbing Mean (SD)	27.59 (18.90)	44.69 (11.03)*	12.39 (8.13)*	28.00 (21.84)	27.33 (17.40)
Percent Nicotine Users	38.24	37.50	38.89	100.00	0.00
Daily Nicotine Use Mean (SD)	2.96 (4.96)	2.70 (4.53)	3.19 (5.42)	7.75 (5.23) †	0.00 (0.00)†
Daily Alcohol Use Mean (SD)	0.72 (0.95)	0.46 (0.69)	0.95 (1.10)	0.45 (0.56)	0.89 (1.11)
Daily Caffeine Use Mean (SD)	1.35 (1.22)	1.23 (1.16)	1.46 (1.28)	1.81 (1.48)	1.06 (0.95)
BDI Mean (SD)	5.32 (4.98)	8.56 (4.80)*	2.44 (3.01)*	6.15 (5.26)	4.81 (4.85)
PSQI Mean (SD)	5.74 (3.65)	8.13 (3.50)*	3.61 (2.20)*	6.31 (4.17)	5.38 (3.34)
CES Mean (SD)	15.47 (10.60)	16.56 (10.58)	14.50 (10.82)	14.69 (10.09)	15.95 (11.12)

*Indicates a significant difference between PTSD and Non-PTSD groups $p \leq 0.05$

†Indicates a significant difference between Nicotine Users and Non-Nicotine Users $p \leq 0.05$

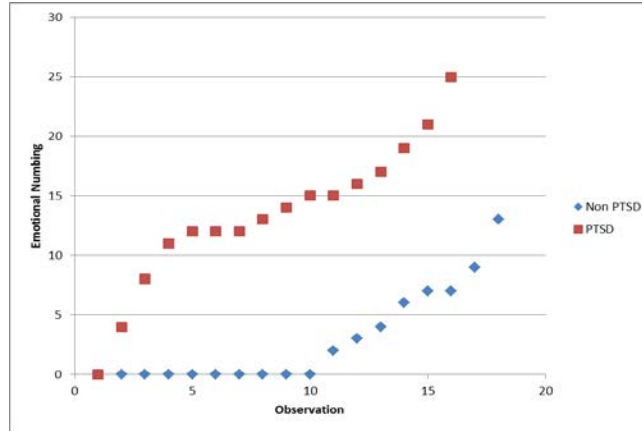


Figure 2. Wake sample emotional numbing scores

3.1.1.2 REM Sample

Twenty seven participants met inclusion criteria and completed a valid [^{18}F]-FDG PET scan during REM. The demographic and clinical characteristics of this sample are summarized in Table 3. Participants were 22 to 40 years old and Caucasian males comprised the majority of the sample. Combat exposure ranged from light to heavy combat, with an average combat exposure of light-moderate ($Mean=15.56$, $SD=10.12$). Average emotional numbing and non-emotional numbing were moderate for the PTSD sample ($Mean=13.33$, $SD=6.28$; and $Mean=42.87$, $SD=11.67$) and low for the non-PTSD sample ($Mean=3.42$, $SD=4.60$; and $Mean=13.83$, $SD=9.38$). Emotional numbing scores ranged from 0-25 in the PTSD sample and 0-13 in the non-PTSD sample. The distribution of emotional numbing scores for each sample is displayed in Figure 3. There were non-significant trends for females to have higher emotional numbing and non-emotional numbing scores than males, and females were significantly more likely than males to receive a diagnosis of PTSD. Within the entire REM sample, average symptoms of depression were mild, with a mean BDI score of 6.04 ($SD= 5.06$) well below the clinical cut off of 13. Sleep difficulties were mild to moderate within the REM sample, with a mean PSQI score

of 6.37 ($SD=3.75$) slightly above the clinical threshold score for good sleep. PTSD patients had moderately poor sleep with a mean PSQI score of 8.07 ($SD=3.63$) versus non-PTSD patients who had relatively good sleep with a mean PSQI score of 4.25 ($SD = 2.77$). Average daily nicotine, alcohol and caffeine use were low within the entire REM sample. A verage daily nicotine use for the nicotine user sample was moderate with a mean of 9.85 doses per day ($SD=8.76$). Because there were only five females and three non-Caucasians in the REM sample, gender and race differences could not be explored.

Table 3. REM sample demographic and clinical characteristics

	Whole Group	PTSD	Non-PTSD	Nicotine Users	Non-Nicotine Users
<i>n</i>	27	15	12	8	19
Age Mean (Range)	29.01 (22-40)	29.11 (22-40)	28.89 (23-37)	29.55 (22-38)	28.79 (22-40)
Percent Females	18.52	33.33*	0.00*	25.00	15.79
Percent Caucasian	88.89	86.67	91.67	100.00	84.21
Percent PTSD	55.56	100.00	0.00	50.00	57.89
Emotional Numbing Mean (SD)	8.93 (7.44)	13.33 (6.28)*	3.42 (4.60)*	9.25 (7.17)	8.79 (7.74)
Non-Emotional Numbing Mean (SD)	29.96 (18.08)	42.87 (11.67)*	13.83 (9.38)*	30.13 (21.83)	29.89 (16.93)
Percent Nicotine Users	29.63	26.67	33.33	100.00	0.00
Daily Nicotine Use Mean (SD)	2.92 (6.45)	1.59 (3.48)	4.57 (8.81)	9.85 (8.76) †	0.00 (0.00) †
Daily Alcohol Use Mean (SD)	0.72 (1.00)	0.42 (0.70)	1.09 (1.21)	0.47 (0.66)	0.82 (1.11)
Daily Caffeine Use Mean (SD)	1.44 (1.29)	1.26 (1.19)	1.67 (1.43)	2.23 (1.66)	1.11 (0.97)
BDI Mean (SD)	6.04 (5.06)	8.53 (4.87)*	2.92 (3.37)*	7.63 (5.63)	5.37 (4.81)
PSQI Mean (SD)	6.37 (3.75)	8.07 (3.63)*	4.25 (2.77)*	8.00 (4.14)	5.68 (3.46)
CES Mean (SD)	15.56 (10.12)	17.20 (10.68)	13.50 (9.42)	15.63 (9.16)	15.53 (10.74)

*Indicates a significant difference between PTSD and Non-PTSD groups $p \leq 0.05$

†Indicates a significant difference between Nicotine Users and Non-Nicotine Users $p \leq 0.05$

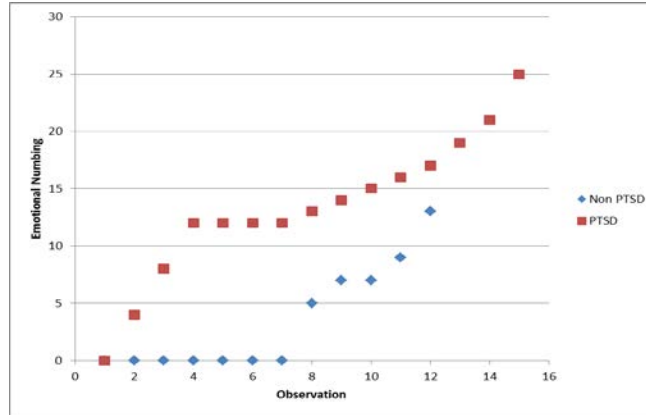


Figure 3. REM sample emotional numbing scores

3.1.2 Correlations Among Variables

Correlations among demographic and clinical variables are summarized in Table 4 for the wake sample and Table 5 for the REM sample. There were significant, moderately strong, positive correlations among emotional numbing, non-emotional numbing, depressive symptoms and poor sleep quality in both samples. There was a significant, moderate, positive correlation between daily average nicotine and caffeine use in the wake sample. This relationship also appeared as a non-significant trend in the REM sample ($p=0.087$). Daily average nicotine and caffeine use were not significantly correlated with emotional numbing, non-emotional numbing, depressive symptoms, or sleep quality in either sample. There was a significant, moderate, negative correlation between daily average alcohol use and non-emotional numbing in the REM sample. This relationship also appeared as a non-significant trend in the wake sample ($p=0.064$). There was also a non-significant trend in both samples of a moderate, negative correlation between daily average alcohol use and emotional numbing ($p=0.082$ in wake, and $p=0.058$ in REM).

Table 4. Correlations among variables in wake sample

	Age	Emotional Numbing	Non-Emotional Numbing	Daily Average Nicotine Use	Daily Average Alcohol Use	Daily Average Caffeine Use	BDI	PSQI	CES
Age	--	--	--	--	--	--	--	--	--
Emotional Numbing	-0.155	--	--	--	--	--	--	--	--
Non-Emotional Numbing	-0.061	0.681*	--	--	--	--	--	--	--
Daily Average Nicotine Use	-0.062	0.061	0.093	--	--	--	--	--	--
Daily Average Alcohol Use	-0.123	-0.303	-0.322	-0.263	--	--	--	--	--
Daily Average Caffeine Use	0.080	-0.249	-0.090	0.338*	0.013	--	--	--	--
BDI	-0.212	0.621*	0.757*	0.280	-0.138	0.155	--	--	--
PSQI	-0.096	0.607*	0.691*	0.067	0.040	-0.027	0.771*	--	--
CES	0.170	0.020	0.141	-0.050	-0.018	0.230	0.131	0.060	--

*p≤ 0.05

Table 5. Correlations among variables in REM sample

	Age	Emotional Numbing	Non-Emotional Numbing	Daily Average Nicotine Use	Daily Average Alcohol Use	Daily Average Caffeine Use	BDI	PSQI	CES
Age	--	--	--	--	--	--	--	--	--
Emotional Numbing	-0.197	--	--	--	--	--	--	--	--
Non-Emotional Numbing	-0.097	0.608*	--	--	--	--	--	--	--
Daily Average Nicotine Use	-0.045	-0.036	-0.031	--	--	--	--	--	--
Daily Average Alcohol Use	0.006	-0.369	-0.391*	-0.256	--	--	--	--	--
Daily Average Caffeine Use	0.305	-0.324	-0.114	0.335	-0.001	--	--	--	--
BDI	-0.103	0.568*	0.760*	0.100	-0.177	0.093	--	--	--
PSQI	-0.055	0.519*	0.620*	0.135	-0.023	-0.030	0.728*	--	--
CES	0.186	0.061	0.231	-0.069	0.068	0.353	0.196	0.062	--

*p≤ 0.05

3.2 REGION OF INTEREST ANALYSES

Results of the ROI analyses are summarized in Table 6. All of the reported clusters were significant at the maximum voxel of significance $p_{\text{uncorr}}=0.01$ level, but none of the clusters were significant at the cluster-level $p_{\text{uncorr}}=0.05$ or $p_{\text{fwe-corr}}=0.05$ levels.

Table 6. Summary of significant clusters in ROI analyses

Direction	Correlate	Wakefulness	k	Z	p_{uncorr}	x, y, z	REM	k	Z	p_{uncorr}	x, y, z
Negative											
EN		Right Striatum	82	2.63	0.004	14, 14, -2	Right Putamen	33	2.42	0.008	26, 20, -2
		Left Putamen	390	2.59	0.005	-28, -10, -2					
		Left Amygdala	20	2.61	0.005	-22, -8, -12					
ENCovNonEN		None	--	--	--	--	None	--	--	--	--
NicAve		Left Striatum	440	2.62	0.004	-14, 16, 0	None	--	--	--	--
Positive											
EN		None	--	--	--	--	Right Caudate	322	2.74	0.003	10, 24, 0
							Left Caudate	104	2.59	0.005	-8, 10, 12
ENCovNonEN		Right Amygdala	38	2.52	0.006	-18, 0, -18	Right Caudate	165	2.34	0.010	14, -6, 18
							Right Amygdala	135	2.69	0.004	22, 0, -20
							Left Amygdala	21	2.82	0.002	-12, -2, -16
NicAve		Right Putamen	23	2.32	0.010	30, 6, -14	None	--	--	--	--
		Left Caudate	26	2.34	0.010	-20, -12, 24					
		Right Amygdala	20	2.37	0.009	34, 4, -20					

EN = Emotional numbing without covariates; ENCovNonEN = Emotional numbing controlling for non-emotional numbing; NicAve = Daily average nicotine use; k = number of voxels included in cluster; Z = test of significance of the maximum voxel of significance within the cluster; x,y,z = MNI coordinates of the maximum voxel of significance

3.2.1 Negative Correlations

During wakefulness, increased emotional numbing was associated with decreased relative rCMRglc in three clusters of continuous voxels located in the right striatum, left putamen, and left amygdala (Figure 4). During REM, increased emotional numbing was only associated with

decreased relative rCMRglc in a single cluster located in the right putamen (Figure 5). After controlling for non-emotional numbing, however, increased emotional numbing was not associated with decreased relative rCMRglc during wakefulness or REM.

During wakefulness, increased daily average nicotine use was associated with decreased relative rCMRglc in a single cluster of continuous voxels located in the left striatum (Figure 6). During REM, however, increased daily average nicotine use was not associated with decreased relative rCMRglc.

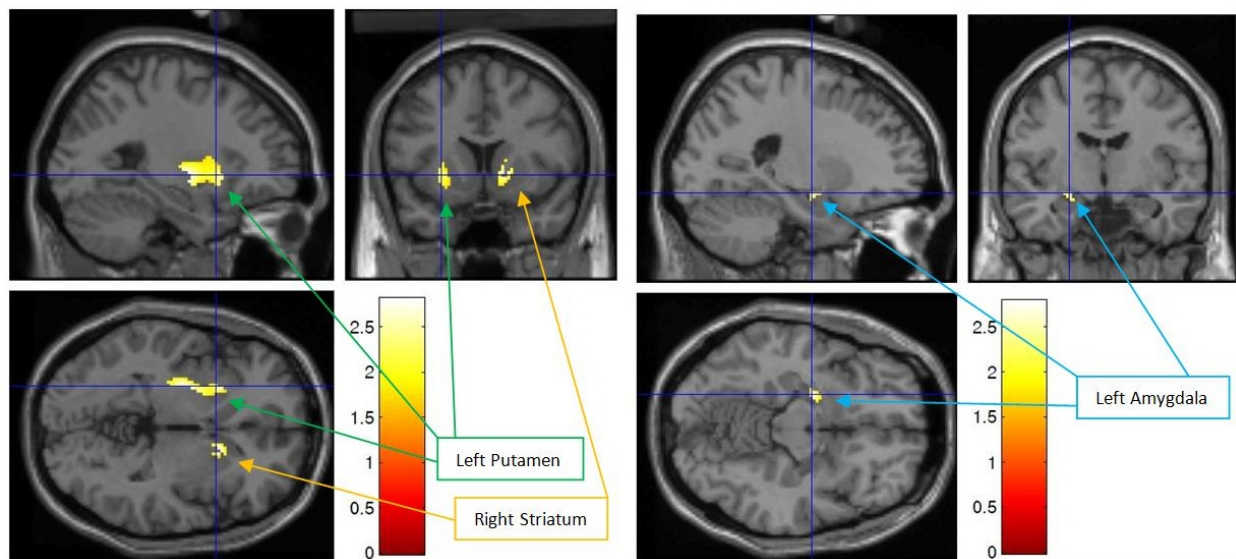


Figure 4. Decreased relative rCMRglc in wake with increased emotional numbing without covariates

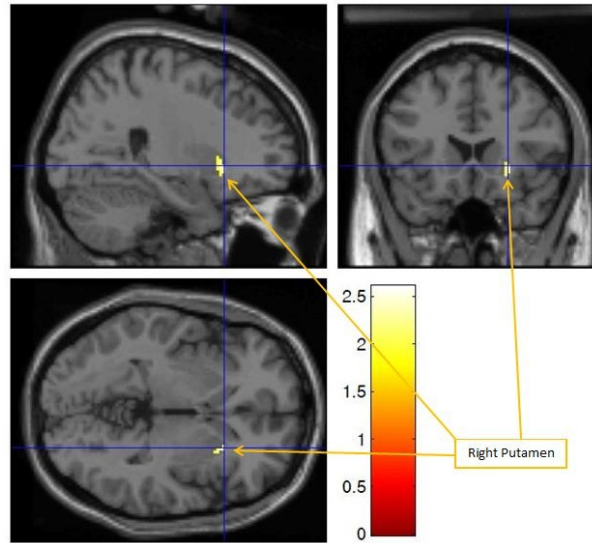


Figure 5. Decreased relative rCMRglc in REM with increased emotional numbing without covariates

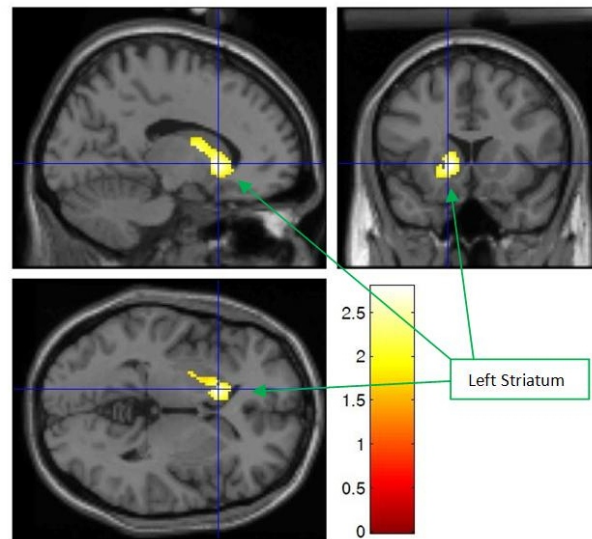


Figure 6. Decreased relative rCMRglc in wake with increased nicotine use

3.2.2 Positive Correlations

During wakefulness, increased emotional numbing was not associated with increased relative rCMRglc. After controlling for non-emotional numbing, however, increased emotional numbing

was associated with increased relative rCMRglc during wakefulness in one cluster located in the right amygdala (Figure 7). During REM, increased emotional numbing was associated with increased relative rCMRglc in two clusters of continuous voxels located in the bilateral caudate (Figure 8). After controlling for non-emotional numbing, increased emotional numbing was associated with increased relative rCMRglc during REM in three clusters located in the right caudate and bilateral amygdala (Figure 9).

During wakefulness, increased daily average nicotine use was associated with increased relative rCMRglc in three clusters located in the right putamen, left caudate, and right amygdala (Figure 10). During REM, however, increased daily average nicotine use was not associated with increased relative rCMRglc.

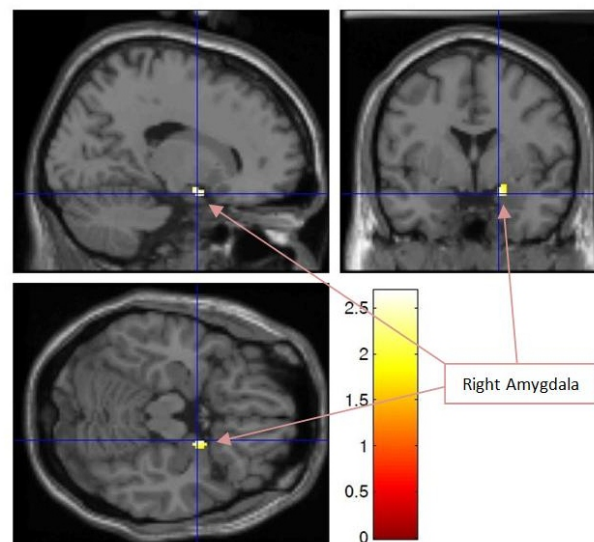


Figure 7. Increased relative rCMRglc in wake with increased emotional numbing controlling for non-emotional numbing

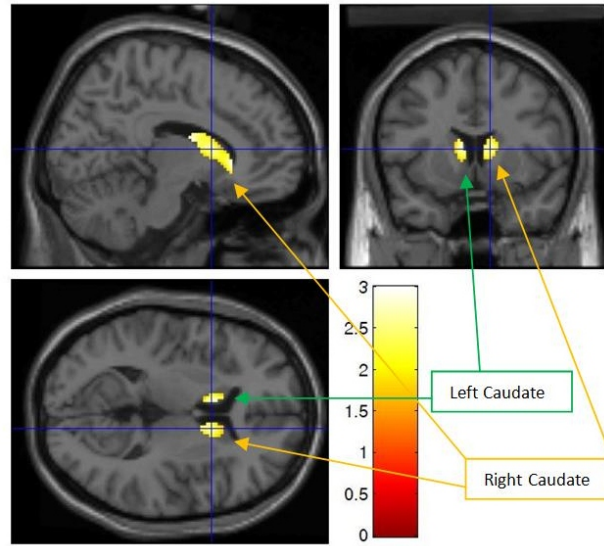


Figure 8. Increased relative rCMRglc in REM with increased emotional numbing without covariates

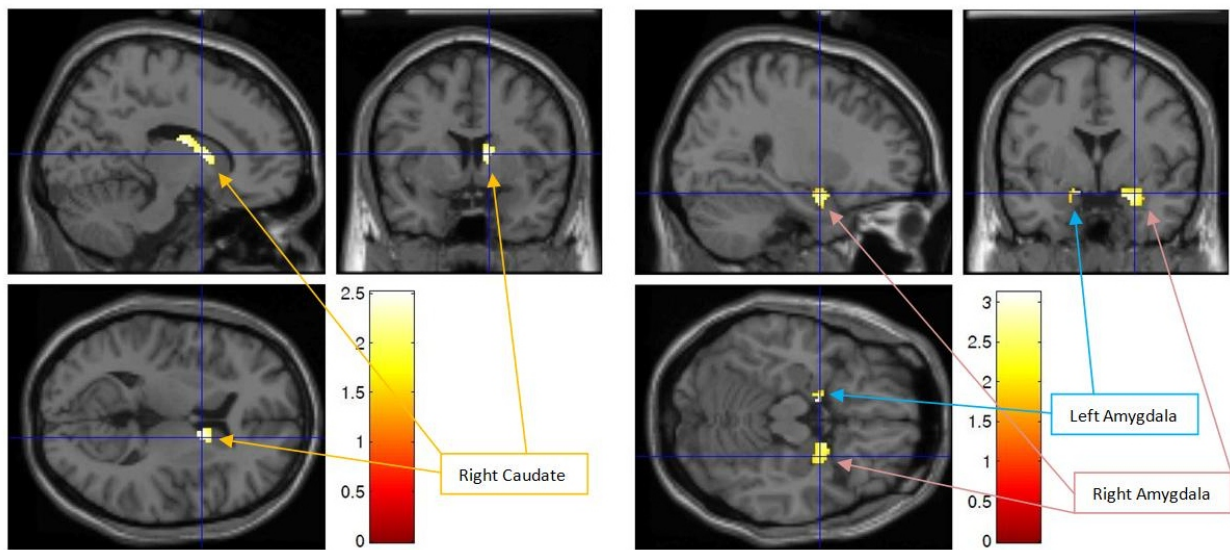


Figure 9. Increased relative rCMRglc in REM with increased emotional numbing controlling for non-emotional numbing

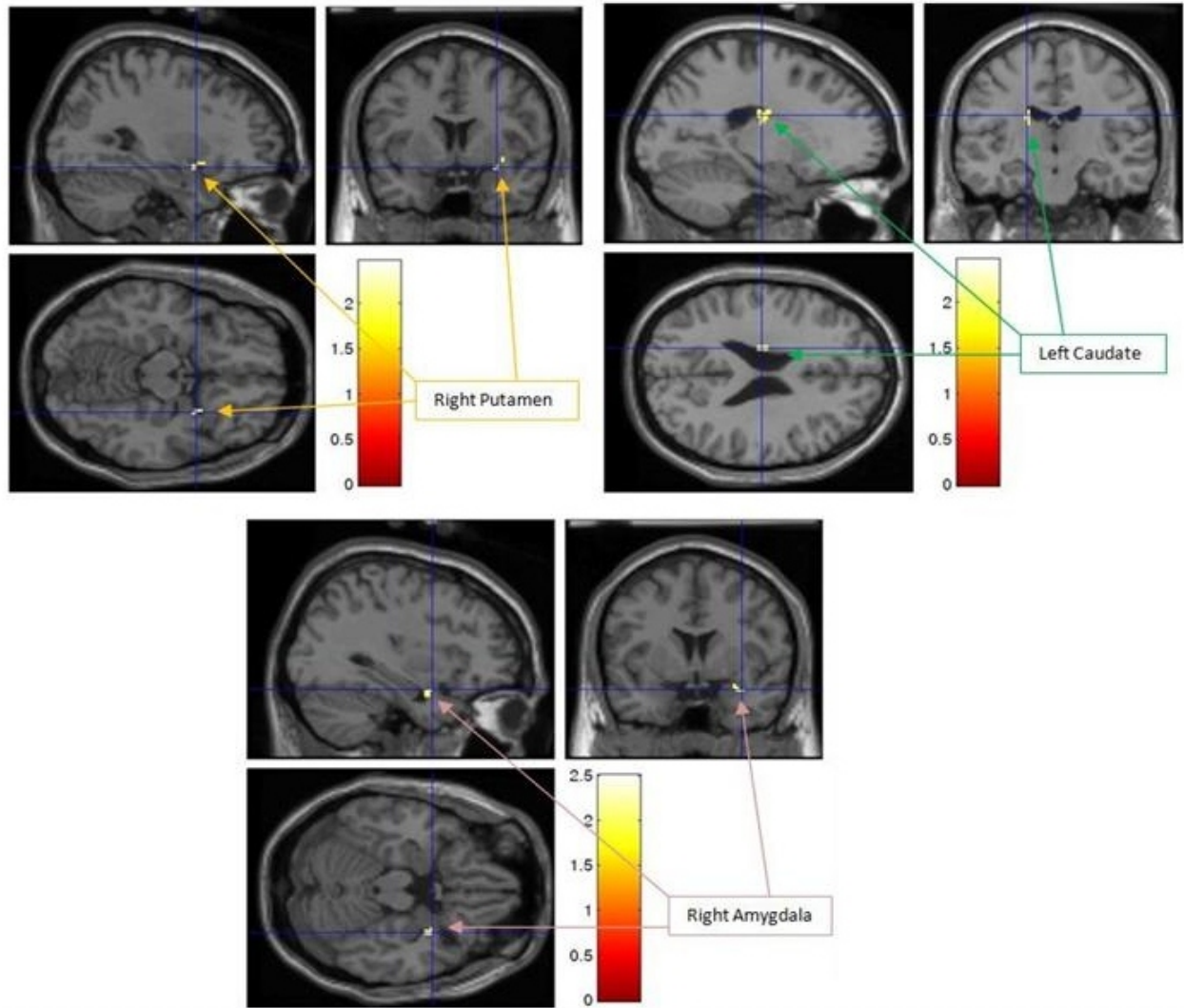


Figure 10. Increased relative rCMRglc in wake with increased nicotine use

4.0 DISCUSSION

This study used [^{18}F]-FDG PET imaging and PSG to examine the neural correlates of emotional numbing and daily average nicotine use during wakefulness and REM in OEF/OIF veterans. Consistent with the a priori hypotheses, ROI analyses revealed that decreased relative rCMRglc was associated with increased emotional numbing in the striatum, particularly during wakefulness in the right striatum and left putamen. Lower baseline activity in these areas of the reward system during wakefulness may indicate a higher threshold for stimulating positive emotion and reward processes, consistent with the finding of less activation in response to reward in patients with PTSD (Sailer et al., 2008; Elman et al., 2009). However, this relationship did not appear to be unique to emotional numbing, as controlling for non-emotional numbing removed the associations between decreased relative rCMRglc and increased emotional numbing. Thus the striatum may also be relevant to symptoms of PTSD other than emotional numbing. This study did not control for the other symptom clusters individually, however, so this study cannot provide definitive evidence regarding which other symptoms of PTSD may also be negatively associated with relative rCMRglc in the striatum. Previous research has shown this area may be involved in sleep-wake regulation, and thus potentially also related to the sleep disturbances in PTSD. Similarly, symptoms of hyperarousal and re-experiencing are thought to be closely associated with both emotional numbing and brain structures related to the reward system, which may include the striatum.

Contrary to expectations, ROI analyses also revealed that increased relative rCMRglc in the striatum was associated with increased emotional numbing during REM, specifically in the bilateral caudate. Relative rCMRglc in a small cluster in the right putamen was negatively associated with emotional numbing, but this relationship was much smaller than the positive association and did not survive controlling for non-emotional numbing. The positive relationship appeared to be unique to emotional numbing in the right caudate, as it survived controlling for non-emotional numbing, although as a smaller cluster of continuous voxels. This may be consistent with phasic theories of PTSD symptomology if trauma survivors are potentially more vulnerable to trauma-related cues and re-experiencing symptoms in REM, leading to subsequent daytime emotional numbing. Exposure to trauma-related cues may come from nightmares present in REM, which cannot be actively avoided except by avoiding sleep entirely or awakening at the onset of a nightmare. The natural increase in reward system activity during REM may also trigger a reversal of dysregulation within the reward system, so that activity is more underactivated in wakefulness and more overactivated in REM as emotional numbing and overall PTSD symptoms increase.

Contrary to expectations and previous findings (Kirby et al., 2008; Cook et al., 2009; Greenberg et al., 2012), emotional numbing was not associated with nicotine use in the present sample, which may be due to the relatively low nicotine use among nicotine users. Only two participants consumed the nicotine equivalent of 20 or more cigarettes per day, which was the cut off for the category of heavy smokers previously associated with emotional numbing severity (Cook et al., 2009). The results of the nicotine use analyses should thus be treated with some caution, as they may not be representative of the heaviest smokers. Nonetheless, ROI analyses revealed that decreased relative rCMRglc in wakefulness was associated with increased daily

average nicotine use in the striatum, specifically the left striatum, which was consistent with the hypothesis that patients may try to stimulate an underactive reward system. This also paralleled the finding of a cluster in the left putamen with a negative association between rCMRglc and emotional numbing without covariates, suggesting that underactivity in the left striatum may be involved in both (non-specific) emotional numbing and nicotine use. However, this negative relationship was not present in REM as expected, nor was nicotine use positively associated with rCMRglc in the striatum as was emotional numbing. Furthermore, clusters of increased relative rCMRglc in the striatum, specifically the right putamen and left caudate, and in the right amygdala were also associated with increased daily average nicotine use during wakefulness. However, these clusters were much smaller than the cluster found in the negative correlation, and were on the threshold for significance. There is thus more evidence to support a negative correlation between daily average nicotine use and relative rCMRglc in the striatum than a positive correlation. This evidence tentatively suggests that there may be a relationship between the striatum and nicotine use and emotional numbing, but these results should be treated with caution given the potentially skewed sample of nicotine users and lack of direct correlation between emotional numbing and nicotine use, as well as the lack of parallel findings in REM.

Finally, ROI analyses revealed relatively small but significant clusters within the amygdala that were generally consistent with striatal activity, indicating that the amygdala, which regulates the salience of emotions, may also be related to emotional numbing. In wakefulness, relative rCMRglc in the left amygdala was negatively associated with emotional numbing without covariates, as was the left putamen. In contrast, relative rCMRglc in the right amygdala in wakefulness and the bilateral amygdala in REM was positively associated with emotional numbing after controlling for non-emotional numbing. This finding provides evidence

that the amygdala may be involved in emotional numbing beyond its established role in fear- and anxiety-related symptoms in PTSD.

Results thus indicate that the striatum is an important structure in PTSD pathology, both for emotional numbing and other symptoms of PTSD, and that patterns of underactivity in wakefulness may be reversed as patterns of overactivity in REM as symptoms of emotional numbing increase. Although daily average nicotine use was not associated with emotional numbing, it was associated with decreased relative rCMRglc in the striatum, which is consistent the hypothesis that nicotine users may be trying to stimulate positive experiences in an underactive reward system. Finally, these results indicate that the amygdala, which is associated with the salience of emotional experiences, may play a role in emotional numbing as well as fear- and anxiety-related symptoms in PTSD.

One limitation in the literature on emotional numbing is the heterogeneity in the definitions of emotional numbing that have been used across studies, and the difficulty that this presents for comparing the current results to previous studies. This heterogeneity can be seen, for instance, in the literature on emotional numbing and nicotine use. On the basis of King et al.'s (1998) four-factor model of PTSD, Cook et al. (2009) and Kirby et al. (2008) used the same five symptoms as the current study to define emotional numbing, although Cook et al. (2009) obtained their data from the PTSD Checklist-Military Version and Kirby et al. (2008) obtained their data from the Davidson Trauma Scale. Greenberg et al. (2012) performed their own confirmatory factor analyses on data obtained from the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV, and produced a four-symptom factor for emotional numbing with excluded the amnesia item (which was placed instead with the avoidance symptoms). Other studies examining emotional numbing have used only diminished interest, detachment, and

restricted affect, and either excluded the amnesia and foreshortened future items entirely (e.g. Maguen et al., 2009) or included them in other symptom clusters (e.g. Nunnink et al. (2010), who included amnesia and a sense of foreshortened future in the avoidance cluster). This study chose to define emotional numbing based on the empirical evidence of King et al.'s (1998) four factor model of PTSD, which is also most consistent with the proposed revisions for the creation of a fourth factor of PTSD symptoms in the DSM 5 (www.dsm5.org). The creation of a fourth symptom cluster which closely resembles King et al.'s (1998) emotional numbing cluster will hopefully spur research on the validity of this new symptom cluster, providing a basis for more homogenous definition of emotional numbing in future research, and enabling more valid comparisons across studies of emotional numbing in PTSD. One disadvantage of an emotional numbing definition based on confirmatory factor analysis of PTSD measures, however, is that it may reduce the applicability of the construct to other disorders which are thought to contain an element of emotional numbing, such as major depression and depersonalization disorder.

Future research is needed to verify and expand the results of the current study. This study lacked sufficient power to examine potential gender and race differences, and although smoking was not restricted except during lab stays, heavy smokers were underrepresented, which may have skewed the findings related to nicotine use. This study chose to focus on military veterans due to the current demands for their care, but results should also be replicated in civilian samples. The results do support the hypothesis that increased emotional numbing is associated with dysregulation within the reward system, but future research will need to further elucidate the nature of this dysregulation, particularly the finding that there may be overactivity in the reward system in REM. This may reflect phasic presentation of PTSD symptoms, and the relationships between emotional numbing, the reward system, and the other symptoms of PTSD

ought to be explored, including the potential role of nightmares during REM influencing subsequent daytime emotional numbing. Research should also explore the possibility of other mechanisms contributing to a general dysregulation within the reward system that exaggerates the natural increases and decreases in reward system activity across the sleep-wake cycle. This mechanism may also be related to the mechanisms that contribute to insomnia and other sleep-related difficulties in PTSD. The reward system is thus a promising area of focus for future neurobiological research on PTSD.

Appendix A

EXPLORATORY WHOLE BRAIN ANALYSES

Supplementary findings from the exploratory whole brain correlational analyses are presented individually and summarized in Figure 28.

A.1 RELATIVE rCMR_{GLC} AND EMOTIONAL NUMBING

A.1.1 Negative Correlation

Wakefulness

Decreased relative rCMR_{GLC} during wakefulness was associated with increased emotional numbing in one cluster (A) of 5119 continuous voxels (MNI coordinates of maximum voxel of significance: -32, 52, 4; $Z = 4.26$, $p_{\text{uncorr}} < 0.000$). Cluster A was significant without correction ($p_{\text{uncorr}} = 0.004$) but not when corrected ($p_{\text{fwe-corr}} = 0.152$) and is presented in Figure 11. Cluster A was located in the left hemisphere and included regions of the frontal and temporal lobes, including the middle frontal gyrus; frontal inferior, superior and middle orbital gyri; frontal superior gyrus; frontal inferior triangularis; and the temporal inferior, superior and middle gyri.

Cluster A extended medially into the insula, putamen, hippocampus, pallidum, and amygdala. Cluster A also extended slightly into the parietal inferior gyrus, the occipital inferior and middle gyri, fusiform and the rolandic operculum.

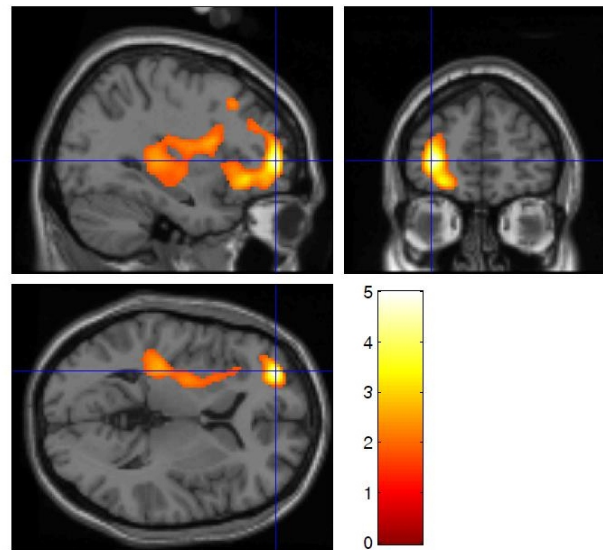


Figure 11. Maximum voxel of significance Cluster A

After controlling for non-emotional numbing, decreased relative rCMRglc during wakefulness was associated with increased emotional numbing in one, smaller cluster (B) of 3526 continuous voxels (MNI coordinates of maximum voxel of significance: -32, 52, 2; $Z = 3.91$, $p_{\text{uncorr}} < 0.000$). Cluster B was significant without correction ($p_{\text{uncorr}} = 0.014$) but not when corrected ($p_{\text{fwe-corr}} = 0.423$) and is presented in Figure 12. Similarly to Cluster A, Cluster B was predominantly in the left hemisphere. Cluster B was located primarily in the left frontal cortex, including regions of the frontal superior medial gyrus; frontal middle and superior gyri; frontal inferior, middle, and superior orbital gyri; and the frontal inferior triangularis. Cluster B also extended slightly into the left insula and midline anterior cingulate cortex.

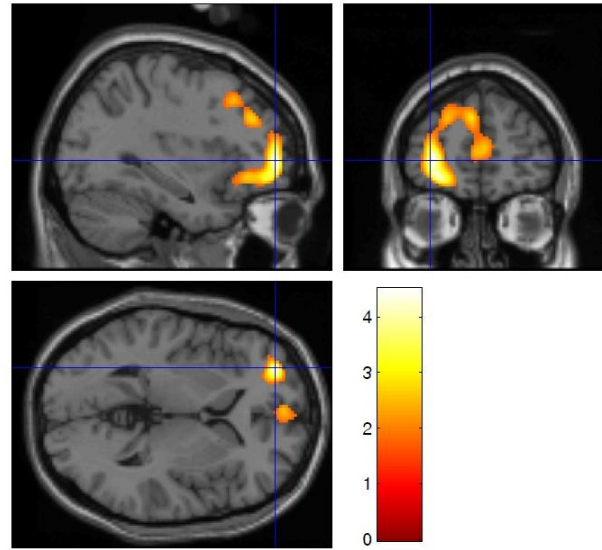


Figure 12. Maximum voxel of significance Cluster B

REM

Decreased relative rCMRglc during REM was associated with increased emotional numbing in one large cluster (C) of 18,578 continuous voxels (MNI coordinates of maximum voxel of significance: 22, 38, -12; $Z = 3.77$; $p_{\text{uncorr}} < 0.000$). Cluster C was significant after correction ($p_{\text{fwe-corr}} < 0.000$), and is presented in Figure 13. Opposite Clusters A and B, Cluster C was predominately located in the right hemisphere. Cluster C was centered in the right temporal lobe, including the right temporal middle, inferior, and superior gyri. Cluster C also included a smaller section of the left temporal superior gyrus; and bilateral Heschl's gyri and fusiform. Cluster C extended anteriorly to the right postcentral, supramarginal, angular and parietal inferior gyri; the right frontal inferior triangularis; right frontal inferior orbital gyrus; right frontal inferior operculum; right precentral gyrus; bilateral frontal middle and superior gyri; bilateral frontal superior medial gyri; bilateral frontal superior, middle and medial orbital gyri; bilateral rolandic operculum and left gyrus rectus. Cluster C extended posteriorly to the right cuneus; bilateral precuneus and lingual gyri; bilateral occipital middle, superior, and inferior gyri; and bilateral

cerebellum. Cluster C also extended to the right putamen; left caudate; and bilateral calcarine; insula; hippocampus; and parahippocampal gyri.

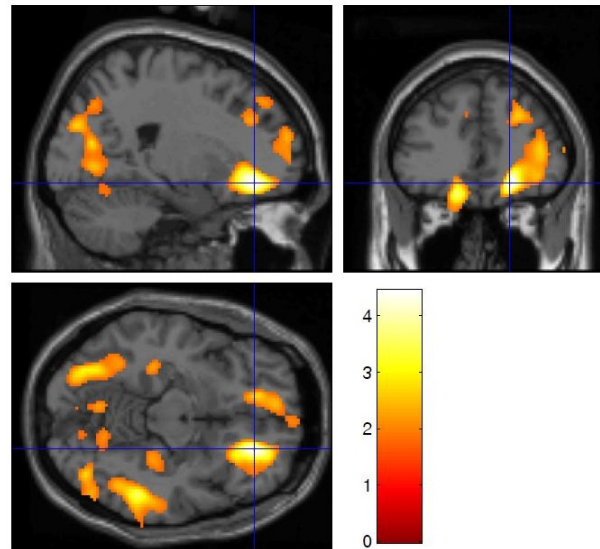


Figure 13. Maximum voxel of significance Cluster C

After controlling for non-emotional numbing, decreased relative rCMRglc during REM was associated with increased emotional numbing in one, smaller cluster (D) of 4727 continuous voxels (MNI coordinates of maximum voxel of significance: 26, 50, 14; $Z = 3.27$, $p_{\text{uncorr}}=0.001$). Cluster D was significant without correction ($p_{\text{uncorr}}=0.007$) but not when corrected ($p_{\text{fwe-corr}}=0.218$), and is presented in Figure 14. Similarly to Cluster C, Cluster D was predominantly located in the right hemisphere. Cluster D included right and midline regions of the frontal cortex, including the right frontal middle and superior gyri; right and midline frontal superior medial gyri; right frontal inferior triangularis; right frontal inferior, middle, and superior orbital gyri; midline frontal medial orbital gyri; and right precentral gyrus. Cluster D extended posteriorly to the right postcentral gyrus and ventrally to the right rolandic operculum. Cluster D also extended ventromedially to the right insula and putamen.

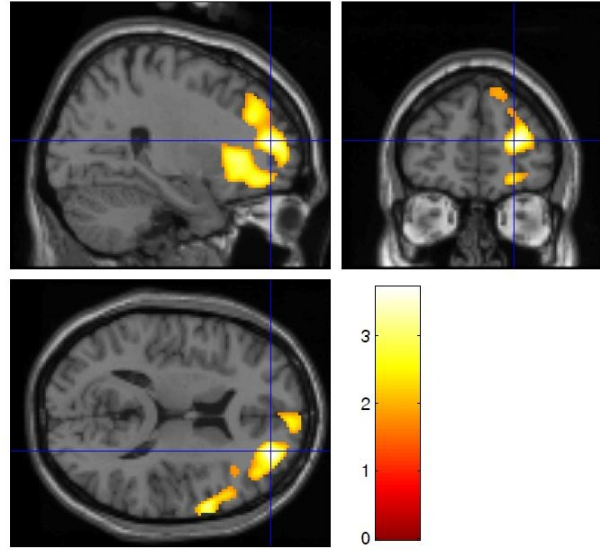


Figure 14. Maximum voxel of significance Cluster D

A.1.2 Positive Correlation

Wakefulness

Increased relative rCMRglc during wakefulness was associated with increased emotional numbing in two separate clusters of continuous voxels, with 3874 voxels in Cluster E and 2092 voxels in Cluster F (MNI coordinates of maximum voxel of significance: -8, -26, 76; $Z = 3.70$, $p_{\text{uncorr}} < 0.000$; and 0, 28, 10; $Z = 3.97$, $p_{\text{uncorr}} < 0.000$, respectively). Clusters E and F were significant without correction ($p_{\text{uncorr}} = 0.011$; and $p_{\text{uncorr}} = 0.050$, respectively) but not when corrected ($p_{\text{fwe-corr}} = 0.342$; and $p_{\text{fwe-corr}} = 0.853$, respectively) and are presented in Figures 15 and 16. Cluster E was centered on the midline region of the central sulcus. Cluster E included bilateral regions of the postcentral and precentral gyri; paracentral lobule; and superior motor area. Cluster E also extended laterally into the left hemisphere, including regions of the frontal middle and superior gyri; and parietal inferior gyrus. Cluster F was located primarily in the

bilateral anterior and middle cingulate cortices, and extended to the midline caudate, and the right frontal superior and frontal superior medial gyri.

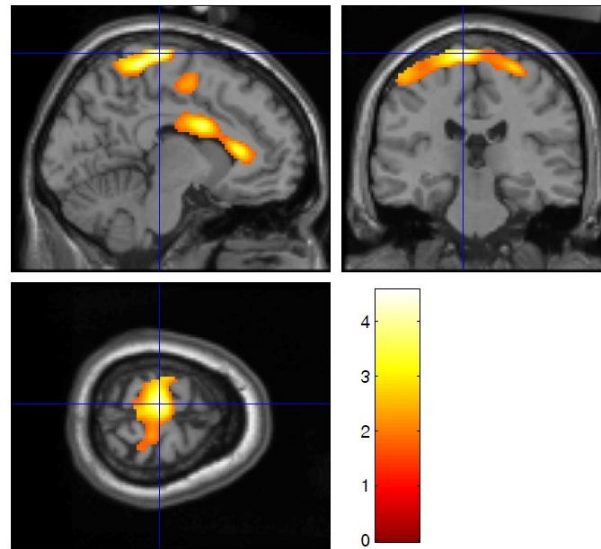


Figure 15. Maximum voxel of significance Cluster E

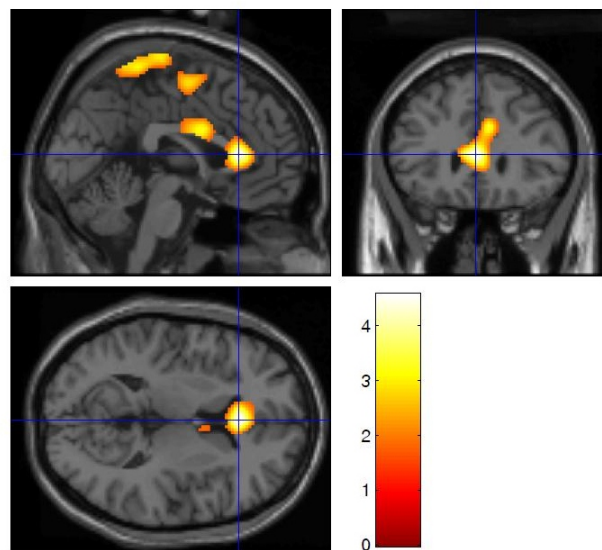


Figure 16. Maximum voxel of significance Cluster F

After controlling for non-emotional numbing, increased relative rCMRglc during wakefulness was associated with increased emotional numbing in two separate clusters (G and H) of continuous voxels, with 3454 and 2939 voxels respectively (MNI coordinates of maximum

voxel of significance: -8, -26, 78; $Z = 4.70$, $p_{\text{uncorr}} < 0.000$; 50, -82, 14, $Z = 2.96$, $p_{\text{uncorr}} = 0.002$, respectively). Clusters G and H were significant without correction ($p_{\text{uncorr}} = 0.015$; and $p_{\text{uncorr}} = 0.023$, respectively) but not when corrected ($p_{\text{fwe-corr}} = 0.442$; and $p_{\text{fwe-corr}} = 0.594$, respectively), and are presented in Figures 17 and 18. Similarly to Cluster E, Cluster G included regions of the left and midline postcentral gyrus; bilateral precentral gyri and paracentral lobule; midline frontal superior gyri; and right superior motor area; and extended slightly into the left parietal superior and inferior gyri and supramarginal gyri. Cluster H was located primarily in the midline occipital lobe, for which there was no equivalent in the uncontrolled analysis. Cluster H included regions of the bilateral calcarine sulci and lingual gyrus; midline occipital middle and inferior gyri with very slight extension into the occipital superior gyri; and midline fusiform and cuneus, with a slight extension to the temporal middle gyrus. There was no equivalent to Cluster F found in the controlled analysis.

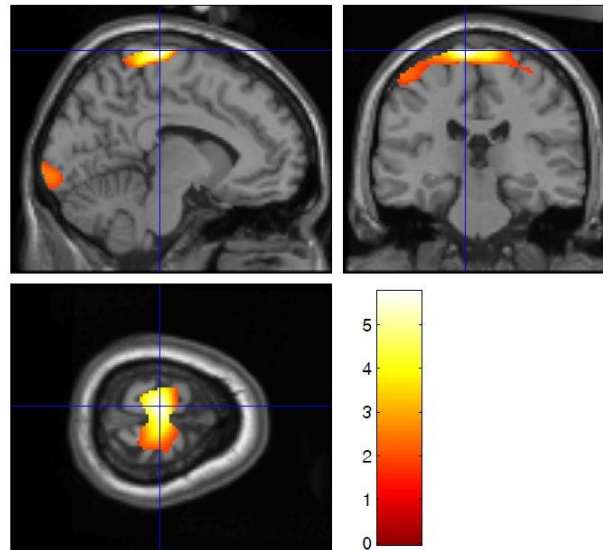


Figure 17. Maximum voxel of significance Cluster G

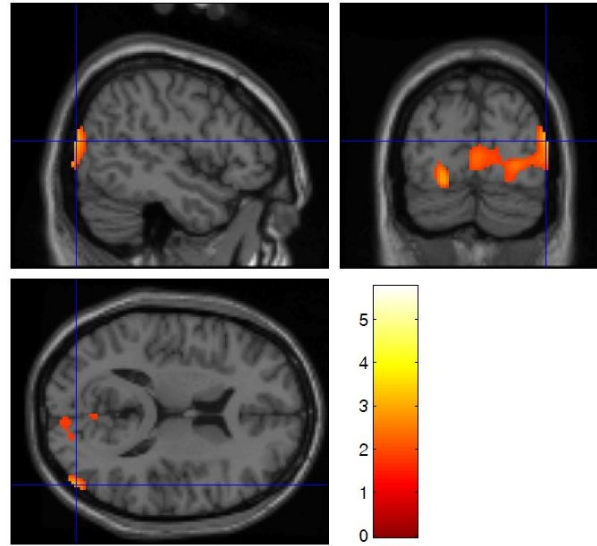


Figure 18. Maximum voxel of significance Cluster H

REM

Increased relative rCMRglc during REM was associated with increased emotional numbing in one cluster (I) of 3231 continuous voxels (MNI coordinates of maximum voxel of significance: -2, 24, 12; $Z = 3.07$, $p_{\text{uncorr}}=0.001$). Cluster I was significant without correction ($p_{\text{uncorr}}=0.021$) but not when corrected ($p_{\text{fwe-corr}}=0.534$) and is presented in Figure 19. Similar to Cluster F in wakefulness, Cluster I was located primarily in the limbic system. Cluster I included midline regions of the anterior and middle cingulate cortices; caudate; and superior motor area. It also extended slightly to the right thalamus.

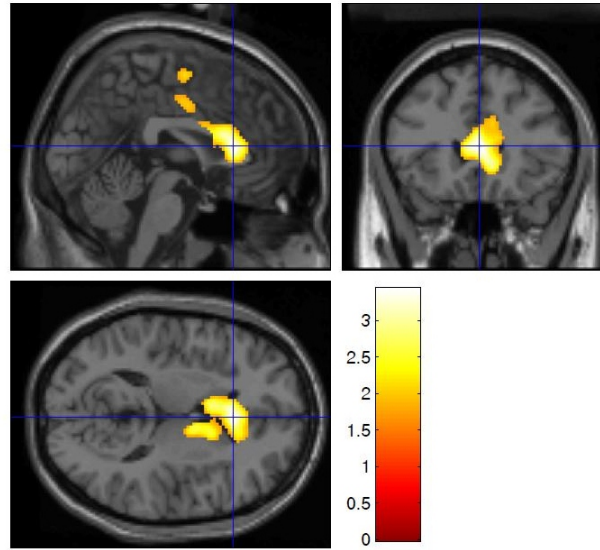


Figure 19. Maximum voxel of significance Cluster I

After controlling for non-emotional numbing, increased relative rCMRglc during REM was associated with increased emotional numbing in three separate clusters (J, K and L) of continuous voxels, with 2893, 2716, and 2375 voxels respectively (MNI coordinates of maximum voxel of significance: 10, -2, 34; $Z = 3.16$, $p_{\text{uncorr}}=0.001$; -14, -36,-10, $Z = 3.77$, $p_{\text{uncorr}}=0.031$; and 8, -32, 72, $Z = 3.03$, $p_{\text{uncorr}}=0.001$, respectively). Clusters J, K and L were significant without correction ($p_{\text{uncorr}}=0.027$; $p_{\text{uncorr}}=0.031$; and $p_{\text{uncorr}}=0.042$, respectively) but not when corrected ($p_{\text{fwe-corr}}=0.631$; $p_{\text{fwe-corr}}=0.685$; and $p_{\text{fwe-corr}}=0.789$, respectively), and are presented in Figures 20, 21 and 22. Similar to Clusters F and I, Cluster J was located primarily in the midline limbic system and included regions of the midline anterior and middle cingulate cortices; midline superior motor area; and left caudate, parahippocampal gyrus, hippocampus, and amygdala; with slight extension to the bilateral olfactory bulbs and right thalamus. Cluster K was located primarily in the left and midline anterior cerebellum and extended into the limbic system. Cluster K included regions of the left and midline anterior cerebellum; midline hippocampus and parahippocampal gyrus; and left fusiform and lingual gyrus. Similar to

Clusters E and G, Cluster L included regions of the left and midline precentral and postcentral gyri; midline paracentral lobule and precuneus; left parietal inferior and superior gyri; and left supramarginal gyrus.

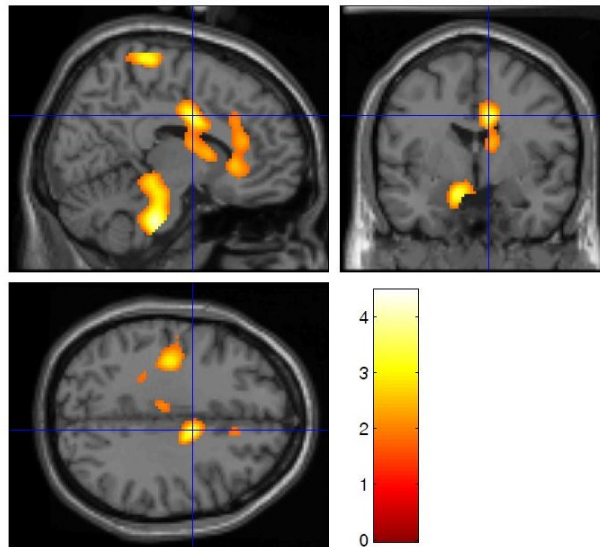


Figure 20. Maximum voxel of significance Cluster J

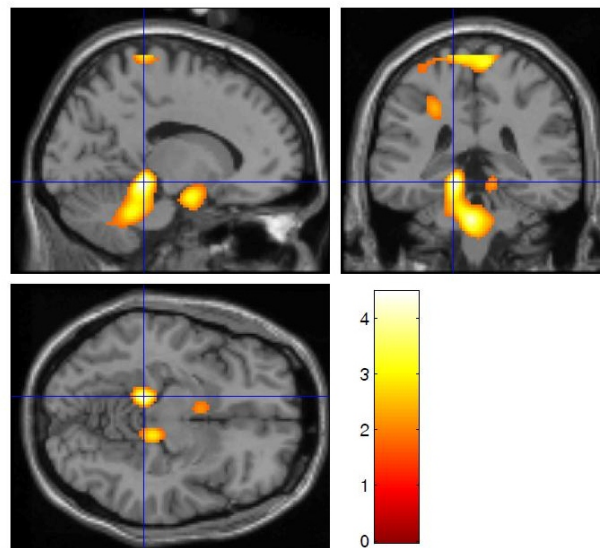


Figure 21. Maximum voxel of significance Cluster K

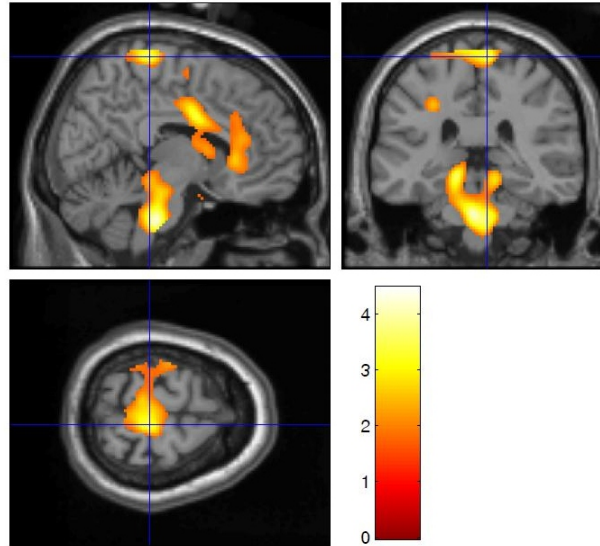


Figure 22. Maximum voxel of significance Cluster L

A.2 RELATIVE $rCMR_{GLC}$ AND NICOTINE USE

A.2.1 Negative Correlation

Wakefulness and REM

Increased daily average nicotine use was not significantly associated with decreased relative $rCMR_{glc}$ during wakefulness or REM.

A.2.2 Positive Correlation

Wakefulness

Increased relative rCMRglc during wakefulness was associated with increased daily average nicotine in three separate clusters (M, N, and O) of continuous voxels, with 5221, 2189, and 2143 voxels respectively (MNI coordinates of maximum voxel of significance: 22, -62, 58; $Z = 3.25$, $p_{\text{uncorr}}=0.001$; -12, -28, 52, $Z = 3.23$, $p_{\text{uncorr}}=0.001$; and 22, 6, 36, $Z = 3.05$, $p_{\text{uncorr}}=0.001$, respectively). Clusters M, N, and O were significant without correction ($p_{\text{uncorr}}=0.004$; $p_{\text{uncorr}}=0.045$; and $p_{\text{uncorr}}=0.047$, respectively) but not when corrected ($p_{\text{fwe-corr}}=0.142$; $p_{\text{fwe-corr}}=0.825$; and $p_{\text{fwe-corr}}=0.838$, respectively), and are presented in Figures 23, 24 and 25. Cluster M was located in the right hemisphere and included regions of the parietal, temporal, and occipital lobes, including the parietal superior and inferior gyri; precentral and postcentral gyri; supramarginal gyrus; angular gyrus, temporal superior and middle gyrus; precuneus; occipital middle and superior gyri. Cluster M also extended slightly to the rolandic operculum and the hippocampus. Cluster N was located laterally from Cluster M in the left hemisphere and included regions of the parietal superior and inferior gyri; postcentral gyrus; precuneus, paracentral lobule, and superior motor area. Cluster N also extended middle cingulate cortex. Cluster O was located bilaterally in the cingulate cortex and frontal lobe and included bilateral regions of the middle and anterior cingulate cortices; superior motor area; and frontal superior medial gyri. Cluster O also extended slightly to the right frontal inferior operculum and frontal superior gyrus.

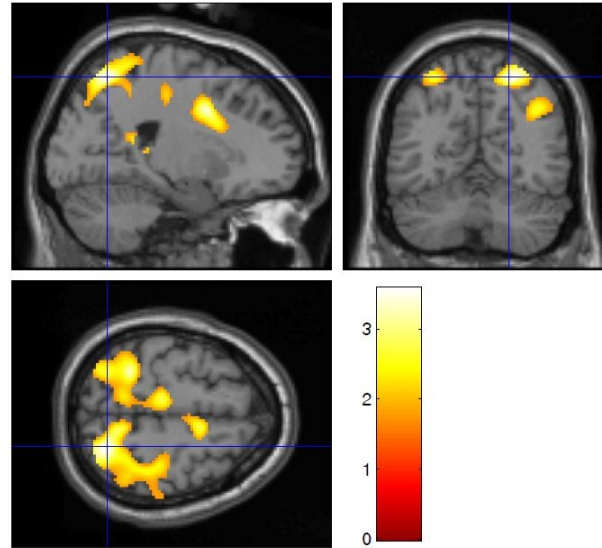


Figure 23. Maximum voxel of significance Cluster M

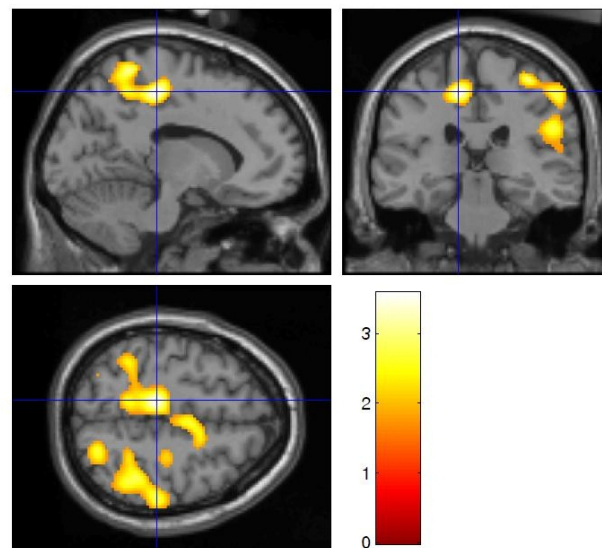


Figure 24. Maximum voxel of significance Cluster N

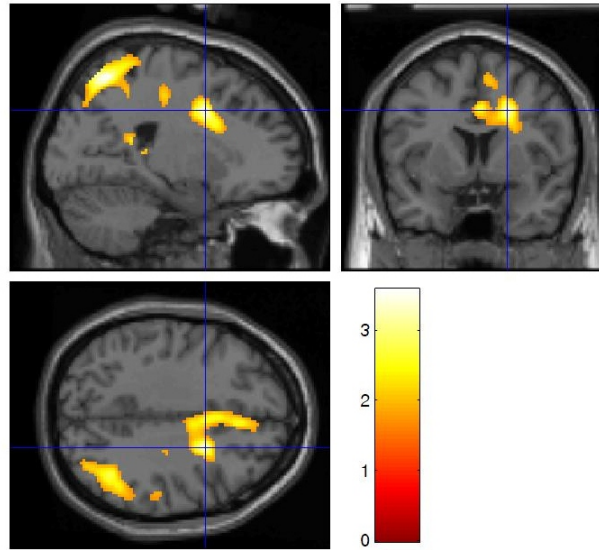


Figure 25. Maximum voxel of significance Cluster O

REM

Increased relative rCMRglc during REM was associated with increased daily average nicotine use in two separate clusters (P and Q) of continuous voxels, with 6519 and 2339 voxels respectively (MNI coordinates of maximum voxel of significance: 20, -38, -32; $Z = 4.62$, $p_{\text{uncorr}}=0.000$; and -10, -24, 56, $Z = 3.84$, $p_{\text{uncorr}}=0.000$, respectively). Clusters P and Q were significant without correction ($p_{\text{uncorr}}=0.002$; and $p_{\text{uncorr}}=0.045$, respectively) but not when corrected ($p_{\text{fwe-corr}}=0.076$; and $p_{\text{fwe-corr}}=0.806$, respectively), and are presented in Figures 26 and 27. Cluster P was located primarily in the right cerebellum and extended to the left cerebellum, bilateral fusiform, and brainstem. Cluster P also extended slightly to the left parahippocampal gyrus; right lingual gyrus; and right temporal inferior gyrus. Similarly to Cluster O in wakefulness, Cluster Q was located primarily in the left and midline cingulate cortex and frontal lobes and included regions of the left and midline middle and anterior cingulate cortices; and superior motor area. Cluster Q also extended to the left paracentral lobule and precuneus; and right frontal superior gyrus.

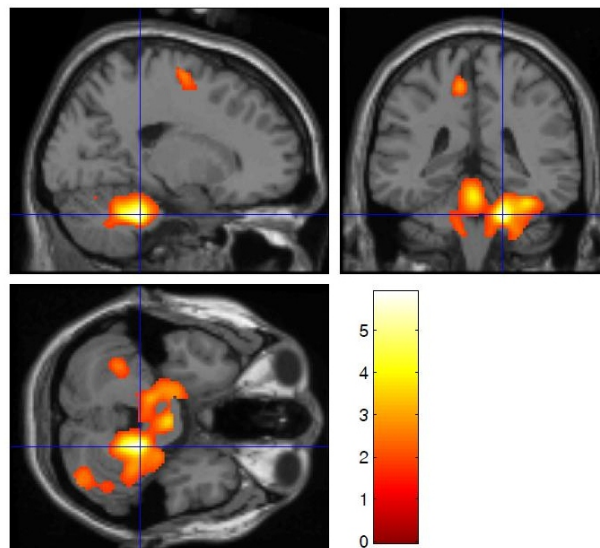


Figure 26. Maximum voxel of significance Cluster P

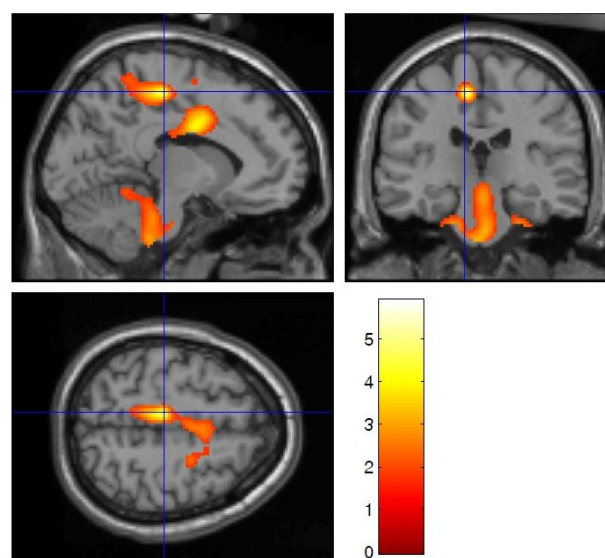


Figure 27. Maximum voxel of significance Cluster Q

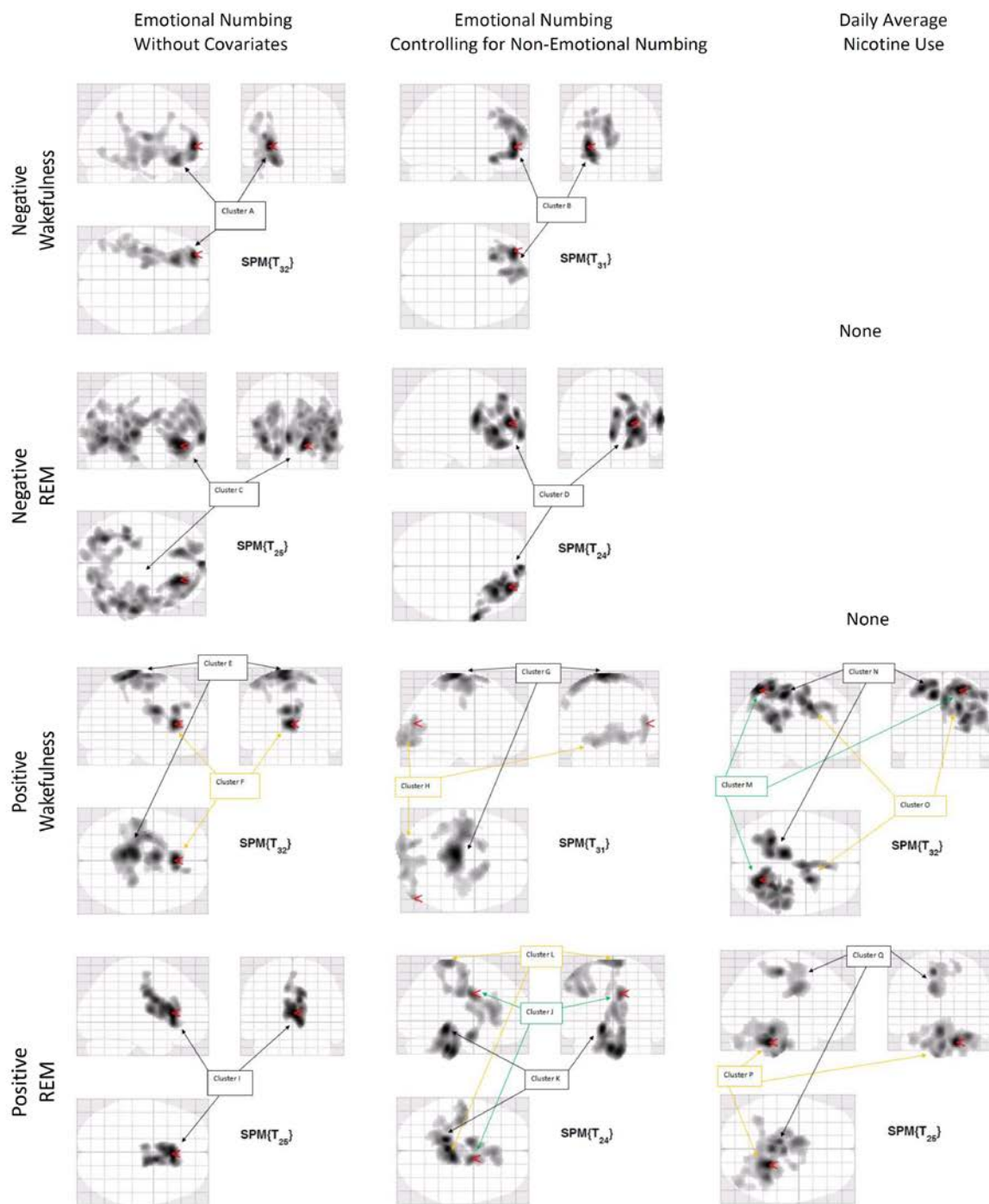


Figure 28. Summary of whole brain analyses

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